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Editor's Choice

Glycaemic control and the risk of mortality in elderly type 2 diabetic patients (ZODIAC-20)

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SUMMARY

Aims: Studies on macrovascular consequences of glucose control in elderly patients (> 75 years) with type 2 diabetes mellitus (T2DM) are lacking. The present study aimed to investigate the relationship between HbA_{1c} and mortality in this specific population. **Methods:** Between 1998 and 1999, 374 primary care patients with T2DM aged older than 75 years participated in the Zwolle Outpatient Diabetes project Integrating Available Care study, a prospective observational study. Early 2009, data on mortality were collected. Updated means for annually measured HbA_{1c} values were calculated after a follow-up time of 10 years. Updated mean HbA_{1c} was used as a time-dependent covariate in a Cox proportional hazard model. Main outcome measures were all-cause and cardiovascular disease (CVD) mortality. Analyses were performed in strata according to diabetes duration (< 5, 5–11 and ≥ 11 years). **Results:** In the group with a diabetes duration < 5 years, an increase of 1% in the updated mean HbA_{1c} level was associated with an increase in all-cause and CVD mortality risk of 51% (95% CI 17–95%) and 72% (95% CI 19–148%), respectively. Glycaemic control was not related to mortality for patients with a diabetes duration ≥ 5 years. **Conclusion:** Poor glycaemic control is related to increased all-cause and CVD mortality in patients > 75 years with T2DM of short duration (< 5 years). **Discussion:** Because of the observational study design, our results should be interpreted with caution. Nevertheless, they are suggestive that improving glycaemic control may be beneficial in elderly patients with T2DM, especially in those with recently diagnosed T2DM. Randomised-controlled trials are necessary to investigate whether this holds true.

What's known

The beneficial effects of improved glycaemic control decrease with longer diabetes duration and with increasing age. However, there are no clinical data on the macrovascular and microvascular consequences of (intensive) glucose control in the very old (patients > 75 years).

What's new

Higher levels of HbA_{1c} are related to increased all-cause and CVD mortality in diabetic patients aged older than 75 years, but only in those with diabetes of short duration (< 5 years). Randomised-controlled trials are necessary to investigate whether improving glycaemic control in specific elderly diabetic populations, for example patients with newly diagnosed T2DM, may be beneficial.

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We declare we have no (financial) conflict of interest.

Introduction

In a recent response to a meta-analysis of the Collaborators on Trials of Lowering Glucose (CONTROL) Group, the differences between patients with type 2 diabetes mellitus (T2DM) of short and long duration were emphasised (1,2). Based on the heterogeneous results of four large randomised-controlled trials, it seems that intensive glucose control is only beneficial in those with diabetes of short duration (3–6). A meta-analysis, published in 2006, already showed that the beneficial effects of improved glycaemic control decreased with longer diabetes duration and with increasing age (7). Unfortunately, there are no clinical data on the macrovascular and microvascular consequences of (intensive) glucose control in adults older than 75 years. Although guidelines recommend applying less stringent targets to frail older adults and those with limited life expectancy, the level of evidence of this advice is low and mainly based on expert opinion (8). We aimed to explore the relationship between HbA_{1c} and (cardiovascular) mortality, and the role of diabetes duration in this relationship, in a prospectively designed cohort of elderly patients (> 75 years) with T2DM.

Patients and methods

Study population

This study is part of the Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC) study; the design and details of which have been presented elsewhere (9). In this study, general practitioners are assisted by hospital-based diabetes specialist nurses in their care of patients with T2DM. At baseline, patients with a very short life expectancy (including

patients with active cancer) or insufficient cognitive abilities were excluded (~5%). Four patients were excluded because of insufficient baseline data. Nearly 90% ($n = 1357$) of the remaining patients agreed to participate. For the present study, we selected all patients aged older than 75 years ($n = 374$).

Data collection

Baseline data were collected in 1998 and 1999, and consisted of a full medical history including macrovascular complications, medication use and tobacco consumption. Patients were considered to have macrovascular complications when they had a history of angina pectoris, myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, stroke or transient ischaemic attack. Laboratory and physical assessment data such as HbA_{1c}, lipid profile, serum creatinine, the urinary albumin-to-creatinine ratio, blood pressure, weight and height were collected annually. An updated mean of annually measured HbA_{1c} was calculated for each individual from baseline to the end of the follow-up period by averaging the baseline values with the mean annual values. For example, at 1 year the updated mean HbA_{1c} is the average of the baseline and 1 year values, and at 3 years it is the average of baseline, 1, 2 and 3 year values. This technique is similar to the one used in the United Kingdom Prospective Diabetes Study (UKPDS) (10).

Clinical endpoints

We examined two clinical endpoints in this study: all-cause and cardiovascular disease (CVD) mortality. Early 2009, the vital status and cause of death were retrieved from records maintained by the hospital and the general practitioners. The causes of death were coded according to The International Classification of Diseases, 9th revision (ICD-9).

Statistical analyses

Continuous variables are presented as mean (± standard deviation) for normally distributed values and as median (interquartile range) for non-normally distributed values. Normality was evaluated using Q–Q plots. Nominal variables are presented as the total number of patients (percentage). A Cox proportional hazard model was used to investigate the relationship between the updated mean HbA_{1c}, as a time-dependent covariate, and mortality with and without adjustment for selected confounders. We used two different models. In model 1, only age and gender were taken into account as possible confounders. In model 2, we adjusted for the following variables: age, gender, smoking (yes or no), BMI, duration of diabetes, serum creatinine, macrovascular complications (yes or no), albuminuria (yes or no), systolic blood pressure, total cholesterol–HDL ratio and use of insulin (yes or no). Analyses were repeated in strata according to diabetes duration. The diabetes duration variable at baseline was categorised into tertiles: < 5 ($n = 111$), 5–11 ($n = 139$) and ≥ 11 years ($n = 124$). In order to estimate the possible implications of higher HbA_{1c} levels on mortality, we calculated the population attributable risk per cent (PAR%) of HbA_{1c} levels $\geq 7\%$ for all-cause and cardiovascular mortality (11). In our analyses PAR% can be interpreted as the percentage by which mortality rates could be reduced if all patients would have had HbA_{1c} levels $< 7\%$. The assumption of proportional hazards was checked by inspecting the Schoenfeld residual plots for the baseline predictor variables. All analyses were performed with SPSS version 15.0.1 (SPSS Inc., Chicago, IL).

Ethics statement

The ZODIAC study and the informed consent procedure were approved by the local medical ethics committee. Informed consent was obtained from all patients.

Results

Baseline characteristics of our study population are presented in Table 1. Approximately one-third of our study population was men. Median age (interquartile range) was 80 (78–83) years and median diabetes duration was 8 (4–13) years. Patients with a diabetes duration ≥ 11 years (tertile 3) had lower mean body mass index and were more often smokers compared with patients with shorter diabetes duration. The number of patients treated with only a diet was the highest in the group with a diabetes duration < 5 years (tertile 1); also, use of insulin was the lowest in this group compared with patients with longer diabetes duration. After a follow-up time of 10 years, 304 of 374 patients (81%) had died, of which 127 deaths (42%) were attributable to cardiovascular causes.

Analyses overall group

In multivariate analyses (model 2), an increase of 1% in HbA_{1c} led to an increase in CVD mortality risk by 26% (95% CI 6–49%). The unadjusted hazard ratio, and the age- and gender-adjusted one, were not relevantly different. The relationship with all-cause mortality was not significant in both models.

Analyses stratified according to diabetes duration (Table 2)

In the group with a diabetes duration < 5 years (tertile 1), the level of HbA_{1c} as a continuous variable

Table 1 Baseline characteristics

Characteristic	Overall *n* = 374	Diabetes duration: Tertile 1 (< 5 years) *n* = 111	Tertile 2 (5–11 years) *n* = 139	Tertile 3 (≥ 11 years) *n* = 124	p-Value
Age (years)	80 (78–83)	80 (78–83)	80 (77–82)	80 (78–84)	0.887
Male sex	130 (34.8)	34 (30.6)	57 (41.0)	39 (31.5)	0.148
Body mass index (kg/m^2)	27.8 (4.4)	28.6 (4.4)	28.0 (4.3)	26.9 (4.2)	0.012
Duration of T2DM (years)	8 (4–13)	2 (1–3)	7 (6–9)	16 (13–20)	–
Systolic blood pressure (mm Hg)	155.7 (24.7)	153.1 (24.3)	156.8 (24.9)	156.7 (24.9)	0.416
Current smoking	33 (8.8)	4 (3.7)	11 (8.0)	18 (14.8)	0.011
HbA1c (%)	7.4 (1.2)	7.3 (1.3)	7.5 (1.1)	7.4 (1.2)	0.292
Albuminuria present	206 (55.1)	53 (47.7)	84 (60.4)	69 (55.6)	0.133
Cholesterol–HDL ratio	4.9 (1.6)	5.2 (1.7)	4.8 (1.6)	4.7 (1.5)	0.099
Serum creatinine (μmol/l)	98 (86–115)	95 (82–111)	99 (87–123)	98 (87–111)	0.165
Macrovascular complications present	162 (43.3)	45 (40.5)	62 (44.6)	55 (44.4)	0.780
Treatment T2DM					
diet	40 (10.7)	19 (17.1)	13 (9.4)	8 (6.5)	0.025
oral glucose lowering agents	265 (70.9)	85 (76.6)	102 (73.4)	78 (62.9)	0.050
insulin	79 (21.1)	7 (6.3)	32 (23.0)	40 (32.3)	<0.001
Receiving antihypertensive treatment	231 (61.8)	71 (65.1)	82 (59.4)	78 (63.9)	0.610
Receiving lipid lowering treatment	17 (4.5)	5 (4.6)	8 (5.8)	4 (3.3)	0.627

Data are means (± SD), medians (interquartile range) or *n* (%). One-way ANOVA, chi-square, or Kruskal–Wallis test was used where appropriate to test for differences between groups.

Table 2 Analyses stratified according to diabetes duration. Hazard ratios and the 95% confidence intervals of HbA_{1c}, for all-cause and cardiovascular disease (CVD) mortality

Mortality	Model	Diabetes duration: Tertile 1 (< 5 years) *n* = 111	Tertile 2 (5–11 years) *n* = 139	Tertile 3 (≥ 11 years) *n* = 124
All-cause	Unadjusted	1.24 (1.01–1.52)	1.01 (0.83–1.24)	0.99 (0.82–1.20)
	Model 1*	1.27 (1.03–1.55)	1.04 (0.85–1.26)	1.03 (0.84–1.26)
	Model 2†	1.51 (1.17–1.95)	1.04 (0.84–1.28)	1.05 (0.85–1.30)
CVD	Unadjusted	1.35 (1.00–1.81)	1.17 (0.87–1.57)	1.19 (0.91–1.55)
	Model 1*	1.37 (1.02–1.84)	1.19 (0.99–1.15)	1.28 (0.98–1.68)
	Model 2†	1.72 (1.19–2.48)	1.18 (0.87–1.60)	1.16 (0.86–1.58)

*Adjusted for age and gender. †Adjusted for age, gender, smoking (yes or no), BMI, duration of diabetes, serum creatinine level, macrovascular complications (yes or no), albuminuria (yes or no), systolic blood pressure, total cholesterol–HDL ratio and use of insulin (yes or no).

was positively related to both all-cause and CVD mortality. In multivariate analyses, an increase of 1% in HbA_{1c} was associated with an increase in all-cause and CVD mortality risk of 51% (95% CI 17–95%) and 72% (95% CI 19–148%), respectively. All results for patients with a diabetes duration ≥ 5 years were not significant.

Population attributable risk per cent

The PAR% of HbA_{1c} levels ≥ 7% for all-cause mortality in patients with diabetes of short duration was 23% (95% CI 2–36%). For CVD mortality the PAR% was 39% (95% CI 17–48%). Again, all results for patients with a diabetes duration ≥ 5 years were not significant.

All analyses were repeated with only the baseline HbA_{1c} value as variable of interest (data not shown). Results did not relevantly change. The proportional hazards assumptions were met for all analyses.

Discussion

Poor glycaemic control is related to increased all-cause and CVD mortality in patients with T2DM aged over 75 years, but only in those with diabetes of short duration. In the lowest tertile (duration < 5 years), the all-cause mortality risk was 51% higher for every 1% increase in HbA_{1c}. For CVD mortality, the increase in mortality risk was even 72%.

To our knowledge, the relationship between HbA_{1c} and mortality in elderly patients with T2DM has not been described before. In previous observational and intervention studies elderly patients were either not included or subanalyses were not performed for this specific population. More recently, a large retrospective observational study showed that there seems to be a U-shaped association between HbA_{1c} and mortality (12). Although an estimated 16% of the study population was aged over 75 years, no subanalyses were performed.

It is important to emphasise that the associations found between HbA_{1c} and mortality in this study do not imply causality. Because of the observational nature of our study, we can only speculate about the underlying mechanisms. Firstly, poor glycaemic control itself may indeed affect mortality risk in elderly patients with recently diagnosed diabetes. The heterogeneous results of four large randomised-controlled trials in younger patients already suggested that intensive glucose control may only be beneficial with regard to mortality in those with diabetes of short duration (1,4–6,13). Secondly, it may be possible that our results are influenced by confounders we did not adjust for. For example, the results for all-cause mortality may be confounded by co-morbidities such as cancer or infectious diseases. In order to reduce the impact of reverse causality we performed additional analyses for the overall group, in which we excluded the deaths in the first year of follow-up. This did not relevantly change the results.

Besides its observational design, there are other reasons why our results should be interpreted with caution. Firstly, our study cohort is rather small and only comprises 374 elderly patients with T2DM. As we also stratified our cohort into tertiles, the number in these tertiles is even smaller. Secondly, the heterogeneous health status of elderly patients makes it more difficult to identify the implications of our results for clinical practice. However, additional analyses revealed that for patients with a diabetes duration < 5 years, the all-cause mortality rate could theoretically have been lowered by 23% if all patients had had HbA1c levels < 7%. An important strength of our study is its prospective design. Other strengths of our study are the high number of deaths after 10 years follow-up, the use of the updated mean method and the number of variables we adjusted for in our model.

Although our study is the first study linking higher levels of HbA_{1c} to increased mortality in elderly patients with recently diagnosed diabetes, we do not recommend aiming for intensive glycaemic control for all subjects in this specific patient category. Intensive control may also lead to an increased risk of hypoglycaemia causing possible adverse events such as fall accidents and fractures. Physicians caring for older patients should take co-morbidity, frailty and estimated life expectancy into account when setting treatment goals for individual patients. Confirmation of our results in other cohorts would be interesting, because if confirmed, randomised-controlled trials are necessary to investigate whether improving glycaemic control in specific elderly diabetic populations, for example patients with newly diagnosed T2DM, may be beneficial.

Author contributions

Concept/design: KJJH, GWDL, NK and HJGB; data collection: KJJH, GWDL, NK and ID; data analysis/interpretation: all authors; statistics: KJJH, GWDL and KHG; drafting article: KJJH; critical revision of article: GWDL, NK, ID, KHG, STH and HJB; supervision: NK, STH and HJB; approval of article: all authors.

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